

Gender Differences in Inflammatory Bowel Disease

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Keywords

Disease activity · Disease course · Disease phenotype · Environmental factors · Epidemiology · Extraintestinal manifestations · Fatigue · Gender · Genetics · Inflammatory bowel disease · Psychological factors · Sex

Abstract

Immune-mediated diseases typically show a female preponderance. Looking at all autoimmune diseases combined, 8 of 10 patients are females. Although not as prominent, gender differences in inflammatory bowel disease (IBD) have been reported for epidemiology, disease presentation, disease course and complications, medical and surgical therapies, adherence, psychosocial functioning, and psychiatric co-disorders. While for some factors evidence is rather good, for others data are conflicting. Gastroenterologists dealing with IBD patients in daily clinical practice should be aware of gender-specific issues for the following reasons: (1) misperception of disease presentation potentially delays IBD diagnosis, which has been shown to have deleterious effects, and (2) awareness of gender-specific symptoms and disease severity allows initiation of early and adequately tailored treatment. This might prevent development of complications. And (3) insights into gender-specific differences in terms of

treatment and adherence to treatment can improve disease management and foster a more individualized treatment approach. In this review, we summarize current knowledge about gender-specific differences in IBD and highlight the most clinically relevant aspects.

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Introduction

The influence of the menstrual cycle on inflammatory bowel disease (IBD) course has been identified >2 decades ago [1]. So far, most sex-specific IBD studies have focused on pregnancy and childbirth. However, many more gender-specific differences (physiological and psychological) seem to play an important role in IBD [2]. Gender-specific differences in IBD have been reported for disease presentation, disease course and complications, medical and surgical therapies, adherence, psychosocial functioning, and psychiatric co-disorders. While for some aspects evidence is rather good, for others data are conflicting. In the era of personalized medicine and in light of potent biological treatment options, it appears adequate to treat patients acknowledging their sex. Within this review, we summarize current knowledge of gender-

specific differences in IBD and IBD management. We further highlight the most clinically relevant gender-specific aspects. Thereby we provide gastroenterologists with a roadmap of how to take gender into account when dealing with IBD patients.

Epidemiology

Immune-mediated diseases typically show a female preponderance. Looking at all autoimmune diseases combined, 8 of 10 patients are females [3–5]. Such female predominance is particularly seen for diseases such as Sjogren's syndrome or systemic lupus erythematosus. In gastrointestinal disease, primary biliary cholangitis and celiac disease are considerably more frequent in women than men. However, gender-specific differences are much less prominent in other immune-mediated disorders such as sarcoidosis, type 1 diabetes, and IBD [5, 6]. Type 1 diabetes indeed is the only major organ-specific autoimmune disorder without a strong female bias; in contrast, a considerable male excess is seen in patients aged 15–40 years [7]. In IBD, gender-specific differences have been reported for Crohn's disease (CD), but not ulcerative colitis (UC), although data are conflicting and possibly depend on geographic areas. In Europe and the United States, CD prevalence appears to be higher in females than in males [8–13], while in Asia the opposite has been observed [14–16]. Early-onset CD (<16 years) has been reported to be more frequent in males than females (20 vs. 12%) [17]. A recent large investigation revealed an even more complex relation between sex and IBD epidemiology [18]. Young females at the age of 10–14 years showed a significantly lower risk for CD compared to men. A reduction in CD incidence of up to 20% has been reported. In contrast, females with an age of 25–29 years and particularly those older than 35 years are more prone to CD compared to their male counterparts. An increased risk of up to 40% has been observed [18]. Older males (>45 years) appear to have a 20% higher incidence rate of UC compared to women [18]. These results have potential clinical implications. Since older male patients are more likely to suffer from the *de novo* UC, this diagnosis has to be considered particularly in elderly men with a chronic colonic inflammation of unknown etiology. However, data on potentially lower rates of IBD in young females should be interpreted cautiously, and diagnostic evaluation should be based on clinical presentation rather than reported incidence rates. This is particularly true in light of the significantly increased diagnostic delay for

female patients [19]. Such a diagnostic delay is a problem in the female IBD population and has potentially deleterious consequences. A diagnostic delay has been associated with increased rates of complications in IBD and higher risk for CD-related intestinal surgery [20].

Environmental Factors

The reasons for the abovementioned gender-specific differences in IBD epidemiology remain unclear; genetic predisposition and different exposition to environmental factors are possible explanations [21]. At least, appendectomy and smoking are associated with an increased risk of CD in females [6, 22, 23]. Smoking has been a well-established and widely accepted risk factor for the development and progression of CD. While traditionally, smoking was more frequently observed in males across all age groups, this picture has changed quite dramatically in recent years. Numbers of smoking females, particularly those at younger age, have been steadily increasing. Currently, the highest smoking rates among IBD patients have been observed in middle-aged female CD subjects. The reported rate of 51.7% is higher than that seen in male counterparts as well as in the age- and sex-matched general population (26.6%) [24]. Accordingly, a Dutch study revealed that more women than men are current smokers in the IBD population [17]. Long time ago, the following dogma was established and has been supported since: smoking is protective in UC, while it has deleterious effects in CD patients. However, the relation between smoking and IBD may be more complex than previously thought. Moreover, it appears to be gender-specific. Cosnes et al. [25] identified a protective effect of smoking in terms of UC development and disease course in male patients only. Moreover, a decrease in the need for immunosuppressive treatment was seen in smoking male patients, but not females [25]. In CD, the deleterious effects of smoking were seen in females, but not in males [25]. Female IBD patients probably have the highest benefit from smoking cessation and should be encouraged to stop smoking, in both UC and CD. Given the excess rates of smoking CD females [24], smoking cessation programs should be targeting those first.

A plethora of other gender-specific environmental factors potentially contribute to the development of IBD and disease complications. There appear to be considerable differences in terms of substance exposure between men and women, such as seen for drugs, chemical substances

related to occupation, sunlight and vitamin D, lifestyle factors including sleep, and shiftwork. However, the specific contribution of these factors to IBD has yet to be determined in more detail. Of note, hormone exposure during childhood, puberty, and menopause/andropause might play a role in IBD pathogenesis and disease course [6]. A clear gender-specific association with IBD has been established for antibiotics and appendectomy. Antibiotic use is more frequently reported among male patients, and boys may develop IBD more often after intake of antibiotics [26]. Appendectomy has been linked to a higher risk of CD in female patients [22]. The microbiome has been increasingly recognized as a key player in the pathogenesis of IBD [27]. Gender-specific differences in the microbiota composition have been described [28]. However, their specific contribution to the development and disease course of IBD remains elusive.

Genetics

Female preponderance appears to be higher in familial compared to sporadic IBD cases (61 vs. 54%) [29]. Moreover, higher female-to-female transmission rates have been identified (compared to female-to-male transmission) [29]. This so-called female imprinting was specifically seen in CD. These findings shed light on a possible gender-specific genetic predisposition. In addition, several known susceptibility gene variants have been linked to a gender-specific risk increase/decrease for IBD. Among those are R30Q DLG5 in CD (male-specific risk), IL-23R variant L310P (protects women, but not men from developing UC), and a single nucleotide polymorphism in the promoter region of IL-10 (increased risk for UC in females) [30–33]. Mechanistic explanations for these differences are however lacking. A further mechanism for gender-specific differences in IBD genetics is related to X-chromosome abnormalities. X-chromosome abnormalities have been increasingly recognized as a possible contributor to autoimmunity [34, 35]. Loss of the X-chromosome in peripheral T- and B-lymphocytes has been associated with various immune-mediated disorders such as primary biliary cholangitis, autoimmune thyroid disease, Reynolds syndrome, and systemic sclerosis [34, 36]. Loss of specific X-linked genes might result in the formation of autoantibodies [36]. If a similar mechanism is involved in IBD remains unknown. Of note and in accordance with this hypothesis, Turner syndrome, a disease where X-monosomy occurs in every cell, is associated with an increased rate of IBD [37].

Disease Activity and Phenotype

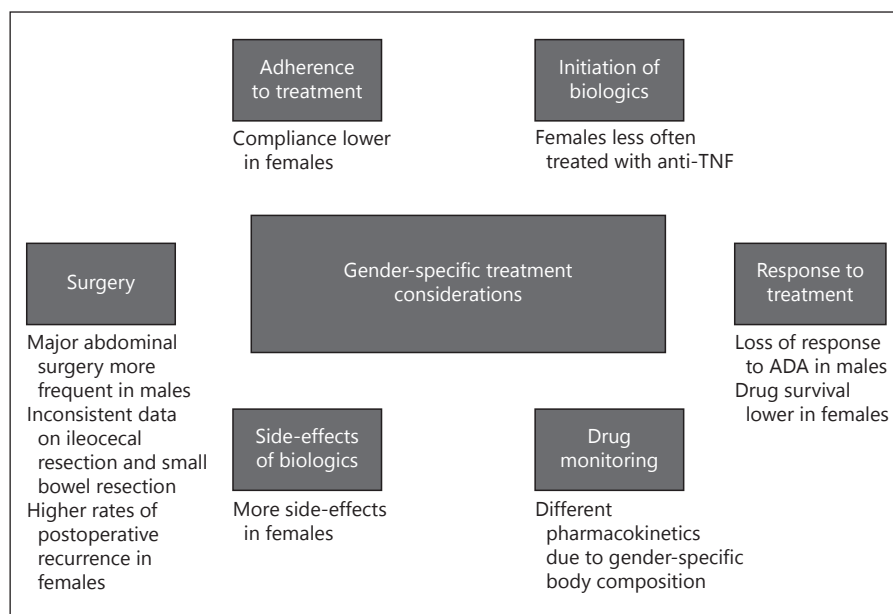
Data regarding the influence of gender on disease activity and disease course are conflicting: in some studies, no association has been found, while in others male sex has been identified as an independent prognostic factor for severe disease [38, 39]. Some studies – however – reported higher rates of remission in males and increased disease activity in females [40, 41]. Data are more consistent when it comes to extraintestinal manifestations (EIM). EIM represent 1 important aspect of disease burden and IBD activity and show a well-established gender-specific distribution. While peripheral joint affections and skin manifestations such as erythema nodosum, pyoderma gangrenosum, and eye disorders are more frequently encountered in females, primary sclerosing cholangitis and ankylosing spondylitis are more common in males [42]. Overall, EIM are more common in female IBD patients [17].

IBD phenotype and location also show gender-specific differences. Our Swiss group recently described an association between sex and upper gastrointestinal tract involvement (L4 according to Montreal classification) [43]. Male sex and young age were identified as the main risk factors for the involvement of the upper gastrointestinal tract in CD patients [43]. In another study, male sex has been significantly associated with ileal disease in CD (28 vs. 20% in females) [17]. These findings suggest that IBD presents differently in men and women.

Disease Complications

For some IBD-related complications, a clear association with male or female sex has been reported. Colon cancer is more frequent in male IBD patients [44]. In addition, mortality from colorectal cancer appears to be higher in men than in women [45]. On the other hand, pulmonary complications show a higher mortality in female CD patients [46]. For other complications, gender-specificity is less clear and data are conflicting. A large prospective study from the Netherlands including 1,106 patients with CD and UC and a mean follow-up of 7 years did not identify gender as prognostic factor for the development of IBD complications. These complications included surgery, cumulative medication use, disease recurrence after surgery, and disease severity [38]. In contrast, a smaller study from Israel with 260 CD patients and a follow-up of 12 years revealed 2 independent prognostic factors for the development of complications: smoking and male sex. The latter showed an OR of 2.6 [39]. In line

Fig. 1. Synopsis of gender-specific treatment considerations. ADA, adalimumab.



with these findings, a study from Mayo Clinic revealed male sex as an independent predictive factor for major abdominal surgery including bowel resection and ileocecal resection [47]. The Dutch IBD biobank – however – demonstrated increased rates of small bowel and ileocecal resection in female patients [17].

Osteopenia and osteoporosis represent possible IBD-related complications that are gender-specific. Counterintuitively, osteopenia and osteoporosis were more frequently reported in male (55.9%) than female IBD patients (29.6%) in a retrospective single-center study from Germany (with dual-energy X-ray absorptiometry scans available for 174 patients). The gender-specific difference was mainly due to different rates of osteopenia rather than osteoporosis [48]. Similar findings have been reported in studies from Japan, the UK, and the Netherlands. Screening for the presence of osteopenia and osteoporosis is important in IBD patients and recommended by current society guidelines. Based on these findings, screening should be particularly promoted in male patients. However, a recent analysis of the Swiss IBD cohort revealed widely differing screening rates with rates as low as 11% in some centers [49].

Treatment and Adherence

Gender-specific differences are most impactful when it comes to IBD management. Indeed, use of and response to IBD treatment seem to vary between men and women

regardless of intestinal disease activity, a fact that raises concerns about an adequate assessment of patients' disease presentation and progression as well as the physician-derived integration of results from diagnostic testing. Although data are limited, the following findings have been reported. Females are considered to receive no specific IBD treatment in a higher proportion than males [40]. In addition to medical treatment, major abdominal surgeries appear to be done more often in men than women, although data on intestinal resection and ileocecal resection are conflicting as previously mentioned [17, 47, 50]. In the Dutch COIN study, there was no large gender-specific difference regarding IBD treatment. Still, male CD patients received prednisone more often [17].

No clear trend has been identified regarding anti-tumor necrosis factor outcome in 2 studies [51, 52]. However, a shorter time until loss of response has been associated with male sex in patients treated with adalimumab. In addition, dose intensification was more often needed in men than in women [51]. Male gender was identified as an independent predictor of loss of response and need for dose intensification, together with known risk factors such as smoking, family history, isolated colonic disease, EIM, and longer disease duration [51]. In contrast, a more recent investigation with a median follow-up of 6 years revealed that drug survival was higher in males compared to females (48.1 vs. 30.8%, $p = 0.016$). This might be attributed to higher rates of side effects to biologics in females than males [53]. Female

Table 1. Most important aspects that are relevant in daily clinical practice when dealing with gender-specific issues

Dimension	Gender-specific difference
Epidemiology	Higher rates of CD in females in EU and US Higher rates of CD in males in Asia Young females with lower risk for CD, older females with higher risk Older males with higher risk for UC
Environmental factors	Appendectomy and smoking in females Antibiotic use in males
Genetics	Female imprinting in familial IBD Susceptibility gene variants such as IL-23R variant L310P (protects women but not men from getting UC) X-chromosome abnormalities
Disease activity and phenotype	EIM more frequent in females Upper GI involvement in males Ileal disease more frequent in males
Disease complications	Higher risk and mortality for CRC in males Higher mortality of pulmonary complications in females Osteopenia more frequent in males
Treatment	Male gender associated with loss of response to anti-TNF Drug survival higher in males More side-effects to anti-TNF in females Adherence rates lower in females
Psychosocial factors	Depression more frequent in females Self-reported QoL lower in females Fatigue more frequent in females

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; EIM, extraintestinal manifestations; IL, interleukin; CRC, colorectal cancer; TNF, tumor necrosis factor; QoL, quality of life.

gender (together with smoking) was identified as an independent prognostic factor for nonadherence to biological treatment [54]. Neglecting these gender-specific aspects may potentially result in suboptimal treatment of men, women, or both. Figure 1 summarizes factors that need to be considered, when it comes to gender-specific treatment approaches.

Psychological Factors

While data regarding epidemiology, disease course, and treatment can be conflicting, data on psychosocial functioning and psychiatric co-disorders in IBD seem to

be quite consistent. The fact that prevalence of depression in IBD is higher in women than in men is not surprising given comparable results in the general population [55]. Women tend to use the healthcare system more often and absence from work seems to be higher [56]. Self-reported quality of life is lower in females than in males [56–58]. Fatigue represents an important clinical symptom that is often underrecognized among physicians involved in IBD care. Several studies have revealed that fatigue is highly frequent in IBD [59–62]. Of note, there is a well-established gender-specific difference in terms of fatigue: female subjects tend to have a higher prevalence of fatigue and this finding is reported across all age groups (*Swiss IBD cohort study, unpublished data*). These findings are irrespective of the presence or absence of anemia, a typical contributor to the symptoms of fatigue [60]. Moreover, gender-specific difference in the prevalence of fatigue is independent of underlying disease activity [60]. Both frequency and intensity of fatigue are more prominent in the female population. IBD further has a negative impact on body image, more so in females than in males [63, 64]. Reduced sexual activity is more frequently reported in female than male IBD patients (66.3 vs. 40.5%, $p < 0.001$) [64]. It is essential that these aspects are not neglected in daily clinical practice.

Clinical Implications of Gender Differences

The most important aspects that are relevant for gastroenterologists, when dealing with gender-specific issues in daily practice, are summarized in Table 1. In the era of personalized medicine and in light of potent biological treatment options, it may not be adequate anymore to treat patients without acknowledging their sex. Tailored treatment strategies for individual patients are needed, and for this, sex has to be taken into account as an important variable in addition to disease activity, phenotype, location, behavior, presence of complications, EIM, and so on. While sex as a modulating factor in IBD development and progression has been increasingly recognized in recent years, data are as of yet conflicting. Most evident and probably most clinically relevant are the following aspects: (1) smoking is a problem and risk factor particularly in females suffering from CD; (2) osteopenia is more frequently observed in men than women; and (3) side-effects from biologics are higher in females than males, which is presumably among the major driving forces for a lower treatment adherence in women. Based on these findings, clinicians should (1) assess

smoking status in women in particular and encourage smoking cessation in this patient population; (2) screen for osteopenia/osteoporosis especially in male IBD patients; and (3) consider women in particular to be nonadherent to biological treatment. Side-effects should be particularly inquired. These 3 simple recommendations are a first step toward a gender-specific IBD management and will improve patient care.

Disclosure Statement

T.G. has a consulting contract with Sanofi-Aventis, received a travel grant from Falk Pharma GmbH and Vifor, and an unrestricted research grant from Novartis. S.R.V. received consultant fees and unrestricted research grants from Abbott, Ferring, MSD,

Pfizer, Takeda, Tillots, UCB, Vifor and Falk Pharma GmbH. L.B. received consulting fees from Abbvie, MSD, Vifor, Ferring, Pfizer, Shire, Takeda, UCB, Janssen and travel grants from Abbvie, MSD, Vifor, Pfizer, Takeda. No company representative was involved in conception, writing, or financing of this study.

Funding Sources

There is no funding to declare.

Author Contributions

T.G. and L.B. drafted and wrote the manuscript and created tables and figures. C.M., V.P., and S.R.V. provided critical input at any stage of writing and contributed to the literature research.

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